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SOLID INCLUSION COMPLEXES OF CLASS II IMIDAZOLE DERIVATIVE WITH B – CYCLODEXTRIN

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ABSTRACT
Low aqueous solubility of Ketoconazole can be increased by complexing it with β-cyclodextrin. Two systems were prepared i.e. binary complexes prepared with β-cyclodextrin and multicomponent systems (β-cyclodextrin and an acid compound), obtained by spray drying method. The complexes were characterized by X-ray diffractometry and differential scanning calorimetry which showed differences between ketoconazole/cyclodextrin complexes and their corresponding physical mixtures and individual components. The dissolution behavior of KTZ from the physical mixtures, and 1:1 complex is similar to the obtained at pH 5. From the binary system 1:2, it has been not possible to dissolve all the drug (around 80%) and after 30 min, the concentration decreased due to the recrystallization of KTZ in the medium. Both multicomponent complexes show different dissolution profiles. The system prepared with citric acid reach a percentage close to 100% but after 90 min the concentration decreases as above, whereas that prepared with hydrochloric acid, 100%, of the dose dissolved and remained in the solution all during the assay. The solubility of ketoconazole increased significantly with the cyclodextrin complexes.

KEYWORDS: Ketoconazole; β-cyclodextrin ; Phase solubility; Differential Scanning Calorimetry; X ray diffrtaction; BCS Class II .

INTRODUCTION

Ketoconazole (KTZ) is an imidazole antifungal agent suitable for the treatment of candidiasis and other systemic fungal infections. The major drawback in the therapeutic application and efficacy of KTZ as oral dosage forms is its very low aqueous solubility because of its hydrophobic structure. KTZ is a weak base and it can be solubilized only under extremely acidic conditions (Van der Meer *et al*., 1980). Cyclodextrins have been used to improve the poor aqueous solubility of these drugs as well as the poor rate of dissolution from their formulations (Pedersen, 1994). Nevertheless, the usefulness of natural cyclodextrins has been limited by relatively low aqueous solubility particularly,β- cyclodextrin (β-CD). Salt formation with different acids and cyclodextrins in the multicomponent complex has been studied to improve the solubility of these base-type drugs and the solubility of classic binary complexes. Several papers have been published concerning the improvement of the solubility and bioavailability of imidazole derivatives through the formation of binary and multicomponent complexes with cyclodextrins (Szente *et al*., 1995; De Beule, 1996; Fenyvesi *et al*., 1996). The aim of this study was to investigate the influence of the complexation of KTZ with β-CD (either binary or multicomponent complexes) on its solubility in aqueous solutions pH 5 and 6. Phase solubility technique was used to analyze the complexation of KTZ with β-CD in both dissolution media. Spray-dried method was employed to obtain solid complexes of KTZ and β-CD in different molar ratio. X-ray diffractometry, differential scanning calorimetry (DSC) and dissolution studies were then used to investigate the interaction between KTZ, β-CD and an acid compound (citric or hydrochloric acid, in the multicomponent systems) in buffer solutions and in solid state.

MATERIALS AND METHODS

Materials

Ketoconazole is a gift sample obtained from Torrent Pharmaceuticals, Gujrat, India. All other materials and solvents were of analytical reagent grade.

Table No. 1 – Formulations of Ketoconazole and their complexes in different ratios

S.No.	Complex Prepared	Ratio used
1	KTZ: PM (Physical Mixture)	1:1
2	KTZ- βCD	1:1
3	KTZ-βCD	1:2
4	KTZ-βCD-HCL	1:2:2
5	KTZ-βCD-CITRIC ACID	1:2:1

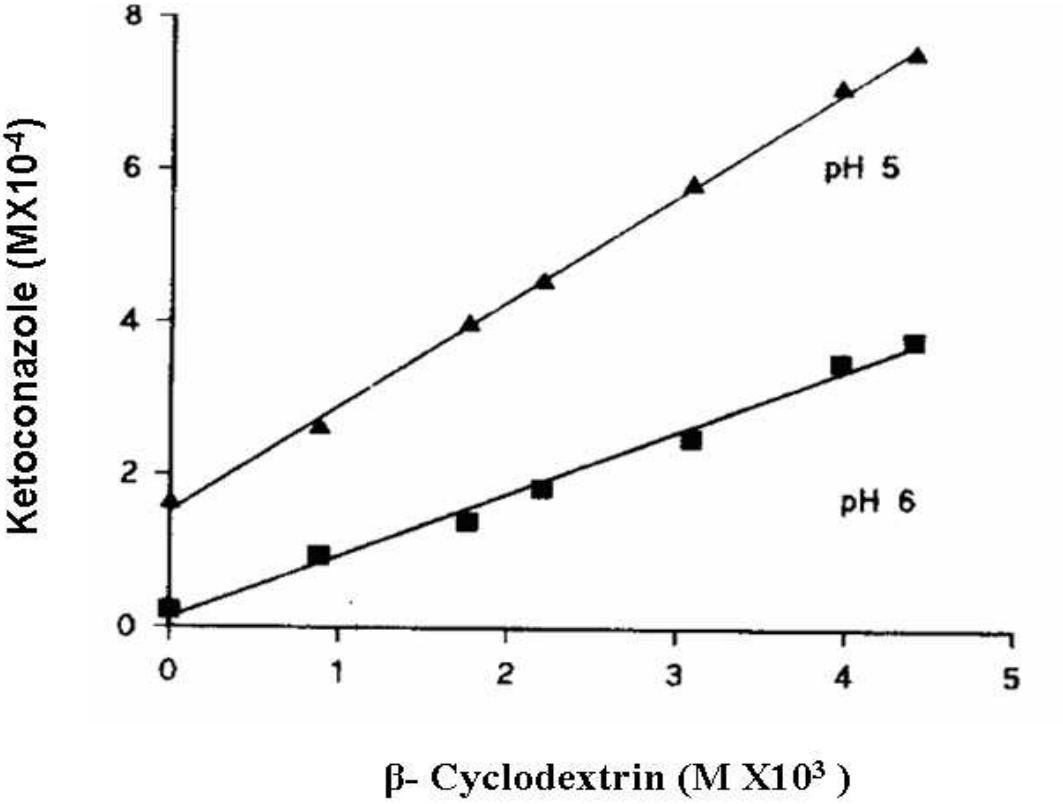

Fig. 1. Phase solubility diagrams of ketoconazole and β-cyclodextrin in buffer pH 5 and 6 at 37°C.

Phase solubility studies

Solubility diagrams were obtained according to Higuchi and Connors (1965) in phosphate buffer solutions of pH 5 and 6. Excess KTZ was added to vials containing various concentrations of β-CD. The vials were shaken in a water bath at 37°C until equilibrium was reached (7 days). The content of each vial was filtered (0.22 pm pore size) and the concentration of KTZ in the filtered solutions was measured by UV spectrophotometry at 225 nm. The apparent stability constant of the KTZ-β-CD complex, assuming 1:1 constant, were calculated from the slope of the initial straight portion of the phase solubility diagrams as

$$KH = slope/S0(1 - slope)$$

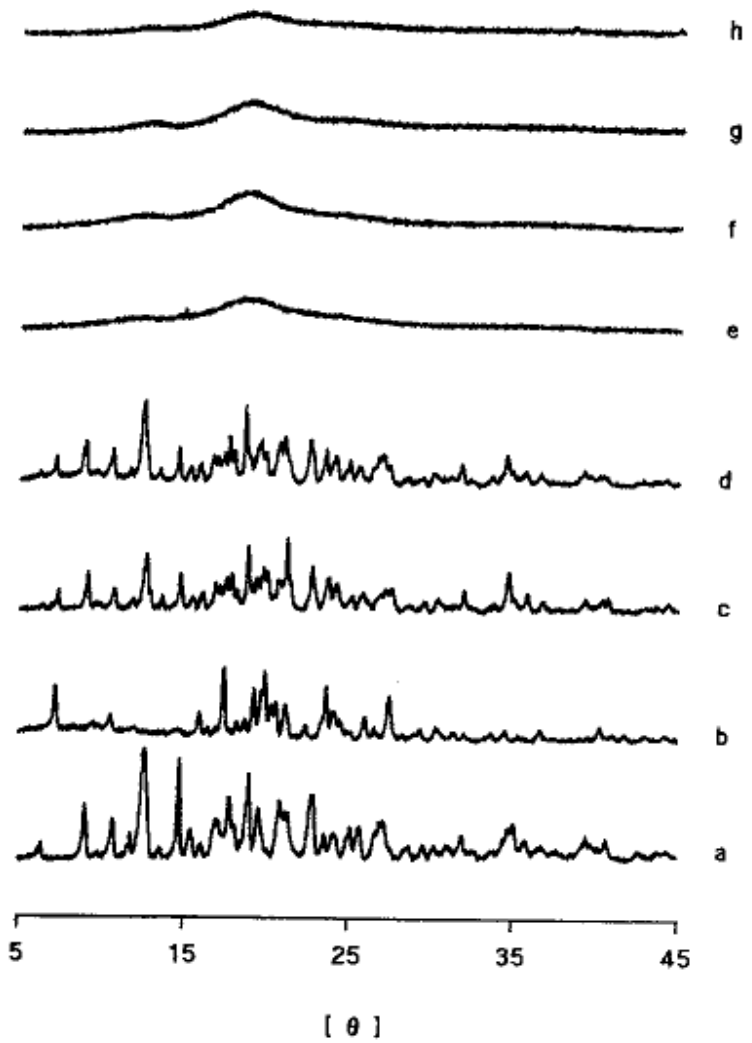

Fig. 2. Powder X-ray diffraction patterns of the different KTZ-βCD systems: (a) βCD; (b) KTZ; (c) physical mixture (1:1); (d) physical mixture (1:2); (e) K TZ-βCD (1 : 1) complex; (f) KTZ-βCD (1:2) complex; (g) KTZ-βCD-HCI (1:2:2) complex; (h) KTZ-βCD-Citric acid (1:2:1) complex.

where So is the solubility of the pure drug (Higuchi and Connors, 1965). All the data are the average of three determinations.

Preparation and characterization of solid inclusion complexes and physical mixtures

The solid complexes of KTZ-β-CD (1:1, 1:2, molar ratio) and KTZ-β-CD with hydrochloric or citric acid (1:2:2, 1:2:1, molar ratio) was prepared using the spray-drying method as follows: KTZ and β-CD in adequate molar ratio dissolved in ethanol and water, respectively, were mixed before spray drying. Multicomponent complexes were obtained from an aqueous solution of KTZ, β-CD and hydrochloric or citric acid. Physical mixtures of an appropriate amount of KTZ and β-CD were obtained by pulverizing and thereafter mixing both solids in a mixer (5 min at 30 rpm). Powder X-ray diffraction patterns were carried out with a Philips X-ray diffractometer (PW 1710 BASED) using Cu-K radiation. Thermal analysis was performed using a Shimadzu DSC-50 system with a differential scanning calorimeter equipped with a computerized data station (scanning rate 10°C/min).

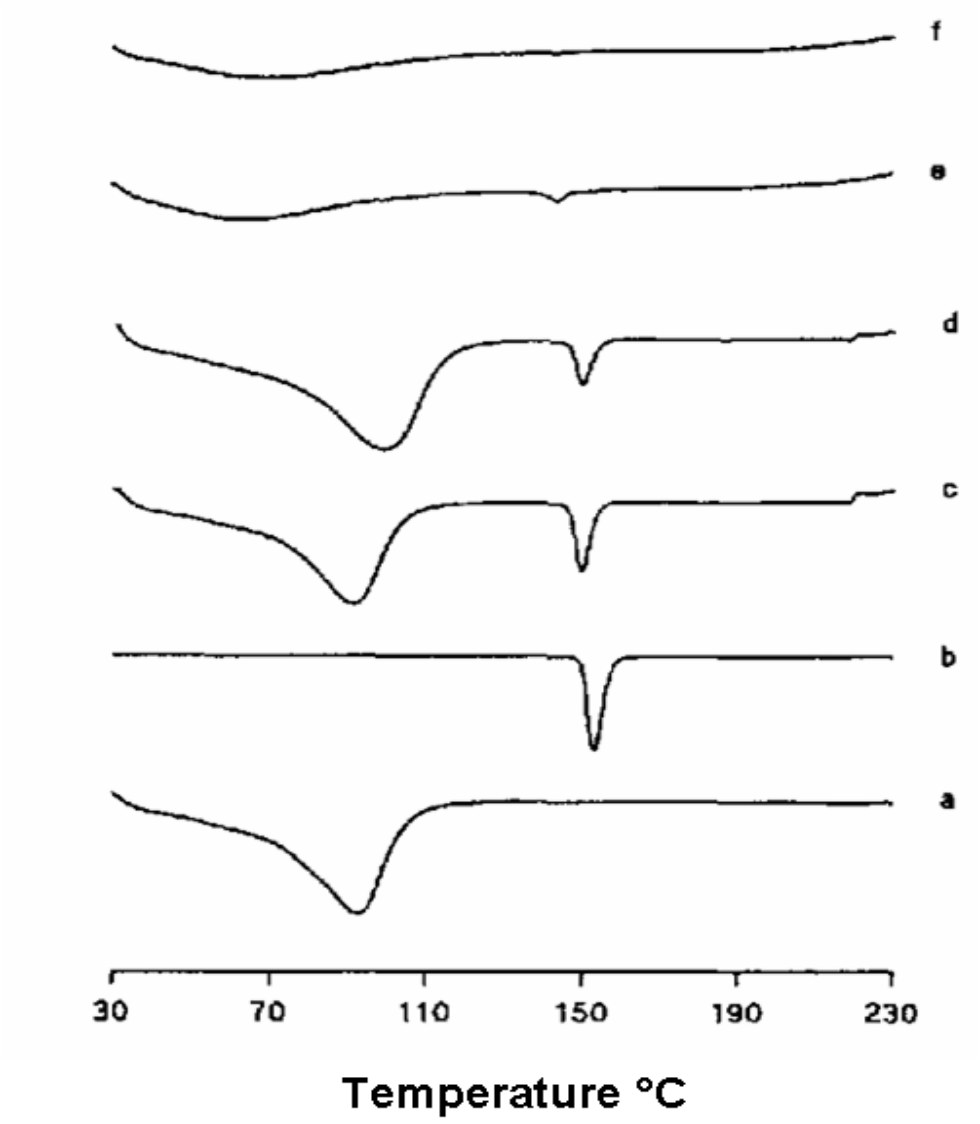

Fig. 3. Differential scanning calorimetry of the different KTZ-βCD systems: (a) βCD; (b) KTZ; (c) physical mixture (1:1); (d) physical mixture (1:2); (e) K TZ-βCD (1 : 1) complex; (f) KTZ-βCD (1:2) complex; (g) KTZ-βCD-HCI (1:2:2) complex; (h) KTZ-βCD-Citric acid (1:2:1) complex

Dissolution studies

Dissolution rates of KTZ, physical mixtures and the inclusion complexes were determined (Nogami *et al* 1969), in phosphate buffer solutions of pH 5 and 6 as the dissolution medium, at 37°C for 180 min. The samples, corresponding to 30 mg of KTZ, were placed in 100 ml of the dissolution medium and shaken at 500 rpm. The concentration of the drug was determined by UV spectrophotometer at 225 nm. All samples were analyzed in triplicate. Dissolution efficiencies after 180 min were calculated (Khan, 1975). The effects of drug formulation on dissolution efficiency at each pH were investigated by one-way analysis of variance with the Scheffe test for multiple comparisons by using graph pad prism software.

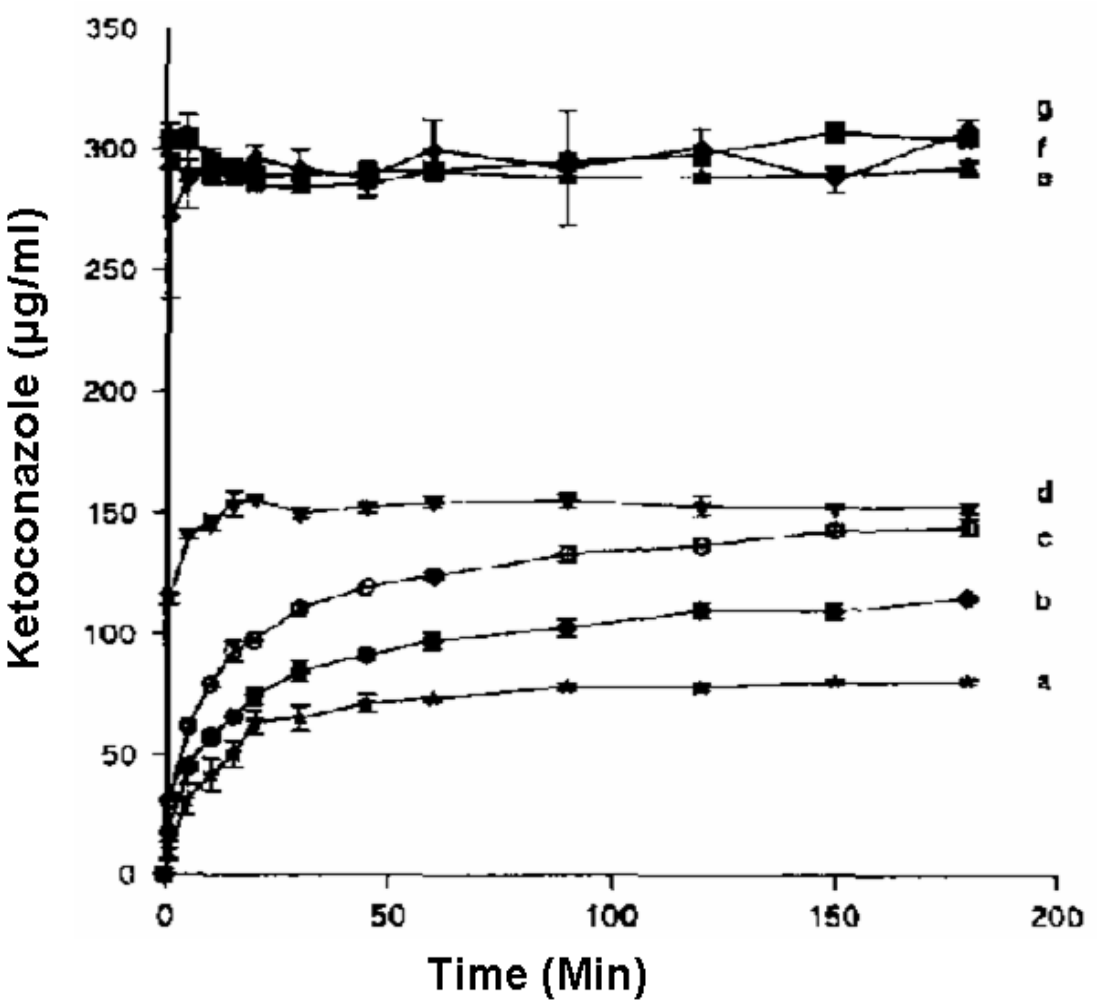

Fig. 4. Dissolution profiles of KET and its inclusion complexes at pH 5: (a) KET; (b) physical mixture (l:1); (c) physical mixture (1:2); (d) KET-BCD (1:1) complex; (e) KET-BCD (1:2) complex; (f) KET-BCD-HCI (1:2:2) complex; (g) KETBCD- Citric acid (1:2:1) complex.

RESULTS AND DISCUSSION

Interaction between KTZ and β-CD in aqueous media

Phase solubility profiles of KTZ with β-CD are shown in Fig. 1. Both diagrams can be classified as A_L type according to Higuchi and Connors (1965). This indicates that the aqueous solubility of the drug increases linearly as a function of β-CD concentration and a soluble complex is formed. Stability constants for the complex calculated from the slope of the initial straight portion of the solubility diagram were 1051.9 M^{-1} at pH 5 and 6959.3 M^{-1} at pH 6. From these values a different interaction in both media between the drug and the cyclodextrin can be deduced. The ionization of ketoconazole decrease with pH and, for this reason, the interaction with β-CD is better at pH 6. Drug cyclodextrin complexation has been found to be better with unionized drug (Otero Espinar *et al*., 1989).

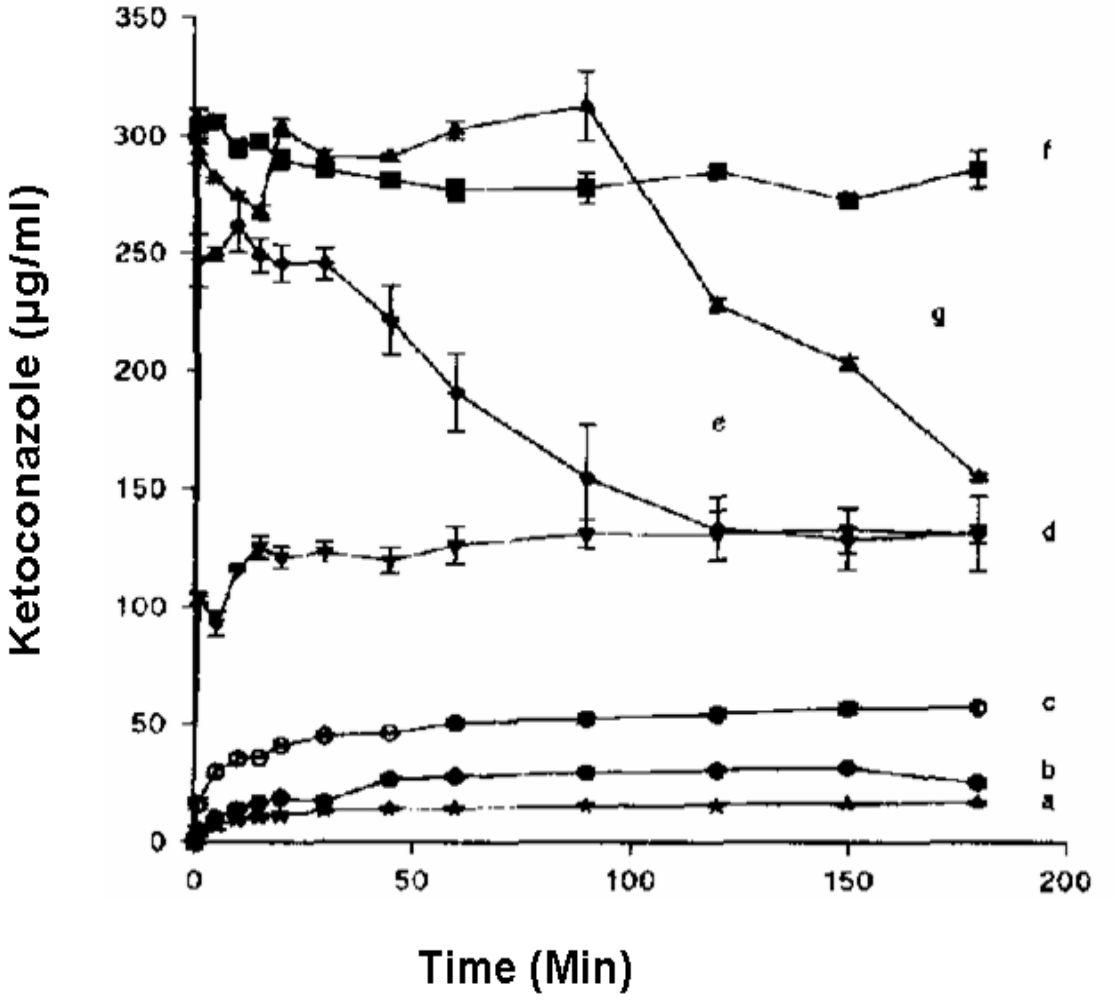

Fig. 5. Dissolution profiles of KET and its inclusion complexes at pH 6: (a) KTZ; (b) physical mixture (1:1); (c) physical mixture (1:2); (d) KTZ-βCD (1:1) complex; (e) KTZ-βCD (1:2) complex; (f) KTZ-βCD-HCl (1:2:2) complex; (g) KTZ- βCD- Citric acid (1:2:1) complex.

Characterization of solid complexes

The X-ray diffractograms of KTZ-βCD binary and multicomponent complexes in comparison with the physical mixtures are shown in the Fig. 2. The diffraction patterns of the physical mixtures correspond to the superimposed diffractograms of KTZ and βCD, while those of the spray-dried complexes show fewer and less intense peaks. This indicates that all spray-dried compounds are markedly less crystalline than the physical mixtures or the pure components. Fig. 3 shows the DSC thermograms of the physical mixtures of the KTZ and βCD as well as those of the solid binary and multicomponent complexes prepared by the spray-drying method. The physical mixtures show two endothermic peaks at 100°C (corresponding to the loss of the water content of βCD) and 149°C (due to melting of the drug). However, these peaks disappeared in the case of all complexes prepared by spray-drying. These results can be explained on the basis of a better interaction among the drug and the cyclodextrin, indicating the complexation of KTZ with βCD. X-ray and DSC studies indicate the formation of amorphous complexes between the cyclodextrin and the drug.

Effects of complexation on dissolution of the drug

Fig. 4 illustrates the dissolution profiles obtained with pure KTZ, physical mixtures and the inclusion complexes in buffer solution pH 5. One-way ANOVA in dissolution efficiency (0-180 min) reveals significant differences between the different formulations ($F_{(6, 14)}$ = 2379.708, α< 0.01). The Sheffe test grouped the formulations are given in table no. 1. Physical mixtures of KTZ with βCD showed a higher dissolution rate than pure KTZ and, this effect increases with the amount of βCD in the mixture. In the binary systems as the amount of β-CD raises in the complexes, a better dissolution profile is shown. Nevertheless, no differences were found among the binary system 1:2 and the multicomponent complexes, prepared with the same molar ratio of β-CD. This fact is probably due to the ionization of the drug in this medium. In buffer solution pH 6, the behavior of the prepared systems defers from the above at pH 5 (Fig. 5). The solubility of KTZ is lower because ionization decreases. For this reason, total amount of KTZ dissolved from all the preparations is lower than at pH 5. Therefore, in spite of the higher stability constant calculated at pH 6, the effect of cyclodextrins on drug solubility is lower than in the more acidic medium. Analysis of variance indicates that the 'formulation' affects significantly 0-180-min dissolution efficiency ($F_{(6,14)}$= 754.308, α <0.01) and the Sheffe test grouped the systems as follows: KTZ PM 1:1, PM 1:2, KTZ- βCD 1:1, KTZ-βCD 1:2, KTZ-βCD-HC1 1:2:2, KTZ-βCD-CITRIC ACID 1:2:1. The dissolution behavior of KTZ from the physical mixtures, and 1:1 complex is similar to the obtained at pH 5. From the binary system 1:2, it has been not possible to dissolve all the drug (around 80%) and after 30 min, the concentration decreased due to the recrystallization of KTZ in the medium (Szejtli, 1991). Both multicomponent complexes show different dissolution profiles. The system prepared with citric acid reach a percentage close to 100% but after 90 min the concentration decreases as above, whereas that prepared with hydrochloric acid, 100%, of the dose dissolved and remained in the solution all during the assay.

CONCLUSION

Binary and multicomponent inclusion complexes of ketoconazole and β-cyclodextrin can be obtained by spray-drying method. This confers improved drug solubility in both media studied. No differences were found between binary and multicomponent complexes prepared with the same molar ratio (1:2) at pH 5. However, in buffer solution pH 6, inclusion complex formed in the presence of hydrochloric acid resulted in higher solubility enhancement for the drug.

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